



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>6</sup> : C07D 487/04, 471/04, A61K 31/495, C07D 213/56, 213/70, 237/18, 409/04, 405/04, 401/04, 241/12, 213/75, 405/12, 241/20, C07F 9/6561, 9/58 // (C07D 487/04, 239:00, 237:00) (C07D 471/04, 239:00, 221:00)</p>	A1	<p>(11) International Publication Number: <b>WO 98/27098</b></p> <p>(43) International Publication Date: 25 June 1998 (25.06.98)</p>									
<p>(21) International Application Number: PCT/US97/23392</p> <p>(22) International Filing Date: 17 December 1997 (17.12.97)</p> <p>(30) Priority Data:</p> <table border="0"> <tr> <td>60/034,288</td> <td>18 December 1996 (18.12.96)</td> <td>US</td> </tr> <tr> <td>08/822,373</td> <td>20 March 1997 (20.03.97)</td> <td>US</td> </tr> <tr> <td>08/862,925</td> <td>10 June 1997 (10.06.97)</td> <td>US</td> </tr> </table> <p>(71) Applicant (for all designated States except US): VERTEX PHARMACEUTICALS INCORPORATED [US/US]; 130 Waverly Street, Cambridge, MA 02139-4242 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): BEMIS, Guy, W. [US/US]; 256 Appleton Street, Arlington, MA 01574 (US). SALITURO, Francesco, Gerald [US/US]; 25 Baker Drive, Marlborough, MA 01752 (US). DUFFY, John, Patrick [US/US]; 303 Windsor Ridge Drive, Westborough, MA 01581 (US). COCHRAN, John, E. [US/US]; 700 Princeton Boulevard #18, Lowell, MA 01851 (US). HARRINGTON, Edmund, Martin [IE/US]; Apartment #21, 284 Harvard</p>		60/034,288	18 December 1996 (18.12.96)	US	08/822,373	20 March 1997 (20.03.97)	US	08/862,925	10 June 1997 (10.06.97)	US	<p>Street, Cambridge, MA 02139 (US). MURCKO, Mark, A. [US/US]; 520 Marshall Street, Holliston, MA 01746 (US). WILSON, Keith, P. [US/US]; 6 Longwood Drive, Hopkinton, MA 01748 (US). SU, Michael [-/US]; 15 Donna Road, Newton, MA 02159 (US). GALULLO, Vincent, P. [US/US]; 51 Fayette Street, Watertown, MA 02172 (US).</p> <p>(74) Agents: HALEY, James, F., Jr.; Fish &amp; Neave, 1251 Avenue of the Americas, New York, NY 10020-1104 (US) et al.</p> <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b></p> <p><i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
60/034,288	18 December 1996 (18.12.96)	US									
08/822,373	20 March 1997 (20.03.97)	US									
08/862,925	10 June 1997 (10.06.97)	US									
<p>(54) Title: SUBSTITUTED NITROGEN CONTAINING HETEROCYCLES AS INHIBITORS OF p38 PROTEIN KINASE</p> <p>(57) Abstract</p> <p>The present invention relates to inhibitors of p38, a mammalian protein kinase involved cell proliferation, cell death and response to extracellular stimuli. The invention also relates to methods for producing these inhibitors. The invention also provides pharmaceutical compositions comprising the inhibitors of the invention and methods of utilizing those compositions in the treatment and prevention of various disorders.</p>											

# INTERNATIONAL SEARCH REPORT

national Application No  
PCT/US 97/23392

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 6 C07D487/04 C07D471/04 A61K31/495 C07D213/56 C07D213/70 C07D237/18 C07D409/04 C07D405/04 C07D401/04 C07D241/12 C07D213/75 C07D405/12 C07D241/20 C07F9/6561 C07F9/58 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07D A61K C07F Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 31451 A (SMITHKLINE BEECHAM CORPORATION ) 23 November 1995 cited in the application see claims	1-3, 24-37
A	WO 96 21654 A (SMITHKLINE BEECHAM CORPORATION) 18 July 1996 cited in the application see claims	1-3, 24-37
<input type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search  6 April 1998		Date of mailing of the international search report  14. 04. 98
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016		Authorized officer  Henry, J

# INTERNATIONAL SEARCH REPORT

national Application No

PCT/US 97/23392

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 //((C07D487/04,239:00,237:00),(C07D471/04,239:00,221:00))

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

6 April 1998

Date of mailing of the international search report

14. 04. 98

Name and mailing address of the ISA

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Authorized officer

Henry, J

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 97/23392

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: none

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The claims are so broad that for determining the scope of a meaningful international search due account has been taken of rule 33.3 PCT; special emphasis was put on the following subject matter during the international search:

Compounds of claims 16, 17, 22, 23, 25; compounds of the examples and compounds of pages 16-21, 30-34, 40-51,

Remark : Although claims 26-37 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/23392

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9531451 A	23-11-95	US 5559137 A JP 10500413 T	24-09-96 13-01-98
WO 9621654 A	18-07-96	AU 4770496 A CA 2210322 A EP 0802908 A FI 972970 A NO 973231 A PL 321292 A	31-07-96 18-07-96 29-10-97 11-09-97 11-09-97 24-11-97